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Effects of High-Frequency Cranial Electrostimulation on the Rest-Activity Rhythm and Salivary Cortisol in Alzheimer's Disease

A Pilot Study

Erik Scherder[a, b] Dirk Knol[c] Marie-Jose van Tol[d] Eus van Someren[e]
Jan-Berend Deijen[b] Dick Swaab[e] Philip Scheltens[f]

[a]Institute of Human Movement Sciences, University of Groningen, Groningen, [b]Department of Clinical Neuropsychology, Vrije Universiteit, Amsterdam, [c]Department of Clinical Epidemiology and Biostatistics, Vrije Universiteit Medical Center, Amsterdam, [d]Department of Psychiatry, Leiden Universital Medical Center, Leiden, [e]Netherlands Institute for Brain Research, Amsterdam and [f]Department of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands

Key Words
High-frequency cranial electrostimulation · Rest-activity rhythm · Salivary cortisol · Alzheimer's disease

Abstract
Objective: In a previous study, low-frequency (0.5 Hz) cranial electrostimulation (CES) neither improved the rest-activity rhythm nor reduced the level of salivary cortisol in patients with probable Alzheimer's disease (AD). To investigate whether the frequency of CES was responsible for these negative findings, we set out to examine the effects of high-frequency CES on the rest-activity rhythm and salivary cortisol of patients with probable AD. We hypothesized that a decreased level of cortisol would parallel a positive effect of high-frequency CES on nocturnal restlessness in AD patients. ***Methods:*** Twenty AD patients were randomly assigned to an experimental group (n = 10) and a control group (n = 10). The experimental group was treated with high-frequency CES, the control group received sham stimulation, for 30 min a day, during 6 weeks. The rest-activity rhythm was assessed by actigraphy. Level of cortisol was measured by means of salivette tubes. ***Results:*** The rest-activity rhythm and the level of salivary cortisol did not react positively to high-frequency CES. In contrast, both groups showed an increase in the level of cortisol after the 6-week treatment period. ***Conclusions:*** High-frequency CES appeared to be ineffective in AD patients.

In previous studies, transcutaneous electrical nerve stimulation, a type of peripheral nerve stimulation, appeared to strengthen the coupling of the rest-activity rhythm to supposedly stable zeitgebers in patients with Alzheimer's disease (AD) [1, 2]. Moreover, AD patients showed a decrease in nocturnal restlessness. Another type of mild electrical stimulation that is partly mediated by the peripheral nervous system is cranial electrostimulation (CES). It was observed that CES improved sleep quality after 2 weeks of treatment in older people with vascular dementia [3].

Based on the positive effects mentioned above, we examined in a recent study the effects of low-frequency CES on the rest-activity rhythm and salivary cortisol of patients in a relatively early stage of AD [4]. The motivation to apply particularly *low-frequency* stimulation was that this type of stimulation preferably stimulates the locus

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Erik J.A. Scherder, PhD
Department of Human Movement Sciences
University of Groningen, A. Deusinglaan 1
NL–9713 AV Groningen (The Netherlands)
Tel. +313 50 363 2470, Fax +31 50 363 31, E-Mail e.j.a.scherder@rug.nl

coeruleus (LC)/noradrenergic neurotransmitter system [5], which strongly projects to the hypothalamic suprachiasmatic nucleus [6]. Salivary cortisol was included as a dependent variable since an increased level of cortisol is indicative of a hyperactive hypothalamic-pituitary-adrenal axis which could cause sleeplessness [7–9]. The results of that study [4] showed that low-frequency CES did not improve the rest-activity rhythm in AD patients and did not lower the level of salivary cortisol. One explanation might be that it is insufficient to focus treatment particularly on the LC/noradrenergic system whereas also other neurotransmitter systems are affected in AD, e.g. the serotonergic system that originates in the dorsal raphe nucleus (DRN) [10]. Both the LC/noradrenergic and the DRN/serotonergic system project to the basal forebrain cholinergic neurons [11] and the basal forebrain cholinergic neurons project to the hypothalamic suprachiasmatic nucleus [12]. It is of note that the LC and DRN not only project to the basal forebrain, they are also innervated by the basal forebrain. Moreover, the LC and DRN receive projections from the hypothalamus [12]. These mutual connections reflect an integrative system that plays an important role in circadian rhythms [12]. Since the DRN/serotonergic system preferably responds to high-frequency stimulation [13] and the LC/noradrenergic neurons are also able to react to high-frequency stimulation [5], the goal of the present study was to examine the effects of *high-frequency* CES on the circadian rest-activity rhythm in patients with AD.

Similar to the previous CES study in AD [4], also in the present study, it was examined whether the high level of cortisol, indicative of sleeplessness [7–9], would decrease by high-frequency CES.

Materials and Methods

Participants

The sample consisted of 20 subjects, drawn from a sample of 500 institutionalized elderly persons. All subjects met the NINCDS-ADRDA criteria for the clinical diagnosis of probable AD [14] and were in stage 5 of the Global Deterioration Scale, indicative of moderate to severe dementia [15]. Exclusion criteria were a history of psychiatric disorder, alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, epilepsy, disturbances of consciousness, focal brain disorders, and a pacemaker. Level of general cognitive functioning was measured by the Mini-Mental State Examination (MMSE), with a maximum score of 30 [16]. The level of education was quantified on a 5-point Likert-type scale (for details, see Scherder et al. [4]).

Subjects were randomly assigned to an experimental group (n = 10) and a control group (n = 10). The gender of the experimental group (10 women) and the gender of the control group (8 females, 2 males) did not differ significantly ($\chi^2 = 2.22$, d.f. = 1; n.s.). The mean age of the participants of the experimental group (83.70 years) did not differ significantly from the mean age of the control group (84.50 years) [t(18) = 0.38; n.s.]. The mean MMSE score of the experimental group (18.20) was not significantly different from the mean MMSE score of the control group (20) [t(18) = 0.98; n.s.]. There was no significant difference between the level of education of the experimental group (2.70) and the control group (3.30) [t(18) = 1.16; n.s.].

The patients and their families were extensively informed about the aim and procedure of the study and gave their informed written consent to further participate in the study. Before onset of the treatment procedure, a trial treatment was applied to both the experimental and the control group. No negative reactions of the patients were observed. The patients and their relatives were not aware of the group in which they participated (experimental or control group), thus preventing a possible bias. The local Medical Ethics Committee approved the study.

Assessment of the Circadian Rhythms

The Rest-Activity Rhythm

The circadian rest-activity rhythm was assessed noninvasively by an actigraph (Actiwatch, Cambridge Neurotechnology, Cambridge, UK), 24 h a day, for 1 week. The actigraph has the size and shape of a watch, is worn on the dominant wrist, and registers acceleration-induced wrist movements. The actigraph quantifies accelerations due to motor activity of the arm and integrates these over 1-min periods. From the resulting rest-activity rhythms, 3 nonparametric variables were calculated [17], using the Actiwatch Sleep Analysis 2001 software (Cambridge Neurotechnology): (1) interdaily stability (IS), a variable that quantifies the strength of coupling between the rest-activity rhythm and supposedly stable zeitgebers (e.g. meals); (2) intradaily variability (IV), a variable that quantifies the fragmentation of the rhythm, that is, the frequency and extent of transitions between rest and activity, and (3) relative amplitude (RA), a variable that quantifies the difference between the main activity (day) and rest (night) periods.

Salivary Cortisol Measurement

Results of several studies suggest that salivary cortisol is a reliable reflection of cortisol concentrations in blood [18, 19]. It represents cortisol that is not bound to plasma proteins, and, therefore, reflects the biologically active free hormone concentration. Salivary cortisol concentrations were obtained by means of salivette tubes (Sarstedt, Rommelsdorf, Germany). The participants were asked to chew on a cotton-wool swab for about 1 min, which is sufficient to collect enough material for analyses [19]. Sampling took place at 9 different points during 24 h. The first sample took place immediately after the moment of awakening, the final sample was acquired just before the patient went to sleep; for further information about the specific points, see Scherder et al. [4]. All saliva sampling was conducted between 7:28 AM and 11:00 PM. Because the duration of the study was 2 years and the patients were randomly assigned to both groups in parallel, season effects can be disregarded.

Cortisol Analysis

Salivary cortisol was analyzed by a coated-tube radioimmunoassay with the Orion Diagnostica Spectra Cortisol Ria Test (Orion Corporation Orion Diagnostica, Espoo, Finland).

Table 1. Means, standard deviations, and analyses of variance of the three actigraphy variables

Actigraphy	Experimental group						Control group						ANOVA (T1-T2)		Effect size η^2
	pre		post		del		pre		post		del		$F(1, 19)$	p	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD			
IS	0.63	0.14	0.64	0.12	0.59	0.20	0.65	0.16	0.59	0.18	0.62	0.08	0.86	0.37	0.043
IV	1.16	0.19	1.18	0.21	1.28	0.27	1.31	0.32	1.34	0.27	1.15	0.15	0.006	0.94	0.000
RA	0.78	0.09	0.79	0.08	0.77	0.08	0.77	0.14	0.80	0.12	0.83	0.09	0.20	0.66	0.01

Procedure

Treatment

CES was applied by the AlphaStim 100, in exactly the same way as in the former low-frequency study [4]. The only difference between both studies was the stimulation frequency: 100 Hz (high-frequency) in the present study versus 0.5 Hz (low-frequency) in the former one. Participants were (sham) stimulated for a period of 6 weeks, 5 days a week, for 30 min each day. For further details, see Scherder et al. [4].

Moments of Measurement

The actigraph and cortisol measurements took place before the 6-week treatment period with (sham) CES (pre), after the 6-week treatment period (post), and again after a treatment-free period of 6 weeks (delayed).

Statistical Analyses

Actigraphy

Multivariate analyses of variance (MANOVAs) with group (treatment and control group) as an independent factor and time [3 levels, i.e. pretreatment: T1; post-treatment: T2, and after a treatment-free period (delayed): T3] as a repeated-measures factor were used to analyze the actigraphic variables. In view of the explorative character of this pilot study, data were submitted to interaction F statistics with 1 degree of freedom on the contrasts T1-T2, T2-T3, and T1-T3, even when the MANOVAs yielded no significant interactions between group and time. If significant interactions occurred concerning one or more contrasts, paired within-group t tests would be performed. This appeared not to be the case in the present study (see the Results section). Effect sizes (η^2) were calculated, that is small <0.01, medium <0.6, and large ≥ 0.14.

The Bonferroni correction was applied to the significance level of $p < 0.05$, resulting in a critical value of $p < 0.01$. The SPSS-PC program [20] was used to analyze the data.

Salivary Cortisol Measurements

The (at most) 27 cortisol measures per person were obtained at irregular times between 7.28 AM and 11.00 PM, which makes a repeated-measures analysis of variance inapplicable. In order to model the cortisol values as a periodic function of the time of measurement, multilevel analysis [21] was used in the same way as in the previous study [4]. An advantage of the multilevel modelling is that missing data can be dealt with in a rather easy way. In our data set, we have 473 measurements from the maximum of 540:27 (9 samples at pretreatment, post-treatment, and delayed measurement) × 20 (10 patients in the experimental group, 10 patients in the control group). A second advantage of multilevel modelling is that we can model the daily (24-hour) cyclical pattern of cortisol measures [22].

For a detailed description of the multilevel two-harmonics models to fit the cortisol level of the experimental group and the control group, we refer to the previous low-frequency CES study [4].

Results

Effects of CES on the Rest-Activity Rhythm

Repeated-measures MANOVAs did not reveal significant group × time interaction effects for IS [$F(2, 18) = 0.88$, $p = 0.43$], IV [$F(2, 18) = 3.18$, $p = 0.07$], and RA [$F(2, 18) = 2.63$, $p = 0.10$]. Means and standard deviations are presented in table 1.Interaction F statistics with 1 degree of freedom did not show any significant difference between both groups after the treatment period, i.e. the contrast T1-T2 (pre-post) (table 1).

Effects of CES on Salivary Cortisol

Since the data were not normally distributed, the multilevel model was fitted to the log-transformed data. The parameter estimates of the interaction model are shown in table 2. Data analyses showed that there was no significant interaction effect between group and time, including group × post-treatment (T2) and group × delayed measurement (T3) (likelihood ratio $\chi^2 = 3.32$, d.f. = 2, $p = 0.19$). Because the group × time interaction was not significant, the model was also fitted without interaction. The parameter estimates of this model are also shown in table 2 (no interaction model). The back-transformed mean cortisol curves are shown in figure 1, and the mean cortisol values evaluated at value 0 (at about 11:00 AM) of the periodic function are shown in table 3. As can be seen in figure 1, the minimum cortisol level of 3.51 nmol/l occurred at about 9.39 PM (control group, delayed measurement), whereas the projected maximum

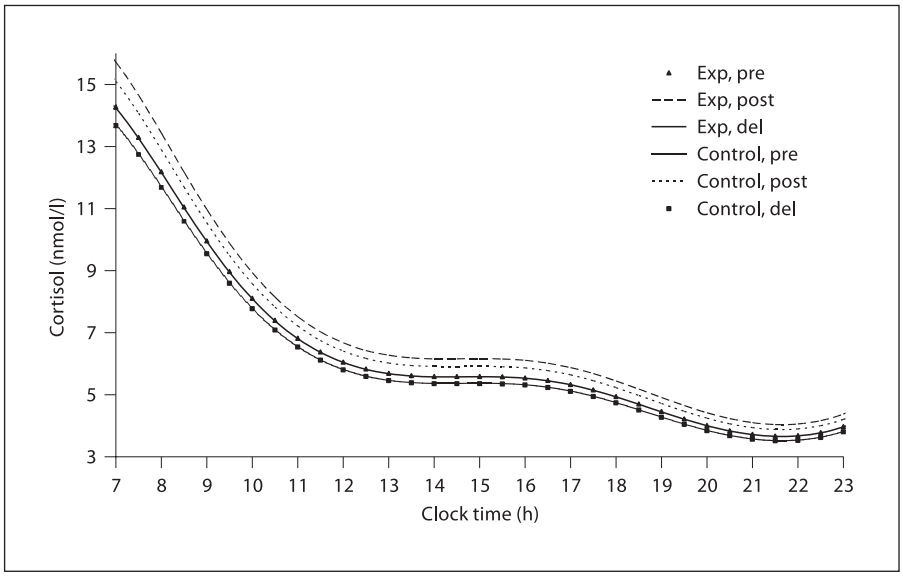

Fig. 1. The fitted multilevel model for the mean values of saliva cortisol of the experimental and control group between 7:00 AM and 11:00 PM.

Table 2. Parameter estimates and standard errors (SE) of the multilevel two-harmonics model to fit the log-transformed cortisol levels in both the experimental group and the control group, at baseline (pre), after a 6-week treatment period (post) and after a 6-week treatment-free period (del)

	Interaction model		No interaction model	
	parameter estimate	SE	parameter estimate	SE
Fixed effects				
Intercept	1.858	0.118	1.879	0.115
Group (treatment vs. control)	0.081	0.145	0.041	0.134
Time				
Post (vs. pre)	0.162	0.067	0.097	0.049
Del (vs. pre)	–0.012	0.068	–0.002	0.051
Group × time				
Group × post	–0.139	0.097		
Group × del	–0.034	0.103		
sin ($2\pi t/24$)	0.566	0.092	0.568	0.092
cos ($2\pi t/24$)	–0.130	0.078	–0.128	0.078
sin ($4\pi t/24$)	0.112	0.067	0.113	0.067
cos ($4\pi t/24$)	–0.248	0.040	–0.246	0.040
Random effects				
Level 2				
var(intercept)	0.086	0.032	0.085	0.032
var(sin ($2\pi t/24$))	0.057	0.028	0.058	0.029
var(cos ($2\pi t/24$))	0.003	0.011	0.002	0.011
cov(intercept, sin ($2\pi t/24$))	–0.029	0.022	–0.029	0.022
cov(intercept, cos ($2\pi t/24$))	–0.0002	0.013	–0.0001	0.013
cov(sin ($2\pi t/24$), cos ($2\pi t/24$))	–0.006	0.013	–0.006	0.013
Level 1				
var(intercept)	0.192	0.013	0.193	0.013
–2 log likelihood	639.87		643.19	

Research question is presented in bold.

Table 3. Mean cortisol levels calculated at value 0 (at 11 AM) for the periodic function before treatment (T1), after treatment (T2) and after a treatment-free period (T3)

Groups	Cortisol levels		
	pretreatment (T1)	post-treatment (T2)	delayed (T3)
Treatment	6.82	7.51	6.81
Control	6.55	7.21	6.53

Treatment is either CES (treatment group) or sham stimulation (control group).

level of 17.02 nmol/l (not shown in fig. 1) was reached at about 5.46 AM (experimental group, post-treatment). For all 6 curves, the ratio of the maximum to the minimum cortisol levels is 4.2. The results on amplitude and peak time should be considered with caution because the maximum cortisol level has been obtained by extrapolation from the fitted curves.

The mean cortisol values indicate that in *both* groups the change in cortisol levels increased in the post-treatment period and returned to their pretreatment values after the 6-week period without treatment (delayed measurement) (fig. 1, table 2 and 3). We tested in this model the main effects of time: likelihood ratio $\chi^2 = 5.15$, d.f. = 2, p = 0.076, n.s. (post vs. pre: z = 1.99, p = 0.047; del vs. pre: z = –0.04, p = 0.96).

Discussion

The results of the present study suggest that, in contrast to our expectations, high-frequency CES did not have a positive influence on the rest-activity rhythm and cortisol levels in AD patients. After the treatment (treatment-free) period of 6 weeks, both the experimental and control group showed hardly any changes in the rest-activity variables IS, IV and RA (table 1). In addition, cortisol levels in both the experimental and control group *increased* instead of decreased after the 6-week treatment period and returned to pretreatment values after the 6-week period without treatment (table 2 and 3, fig. 1).

Although in the present study the lowest cortisol level was observed at about 9:30 PM, an hour before and after that time, the cortisol level was close to this lowest point (fig. 1). These findings approach the results of an earlier study in which 24-hour cortisol profiles of patients with AD were analyzed [23]. In that study, the lowest cortisol level was observed at about 8:00 PM and remained level until midnight, after which the level showed a considerable increase. Compared to this latter finding, the level of salivary cortisol increased about 2 h earlier in the present study. One explanation might be that our patients were institutionalized and preparations for the night are often considered a stressful factor that triggers an increase in cortisol [24].

Considering the absence of treatment effects, together with very small effect sizes with respect to the actigraphy variables IS, IV and RA and the changes in cortisol levels in an opposite direction, clinically relevant treatment effects cannot be expected. In other words, similar to the low-frequency CES study, we must conclude that also high-frequency CES is not effective in AD and research concerning its effects on circadian rhythms in AD should not be continued in its present form.

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